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Cyclophosphamide in systemic sclerosis: Light and shadows

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Pulmonary interstitial fibrosis (PIF) affects half of all patients with systemic sclerosis (SSc) (1) and accounts for one-third of SSc-related deaths (2). Despite enormous efforts, therapy remains empirical and its efficacy is questionable. D-penicillamine (3) interferon-γ (4), and cyclophosphamide (5) have been used to halt the progression of PIF. While studies on these regimens have reported encouraging results, patients still die from respiratory failure due to PIF. For instance, D-penicillamine was shown to have beneficial effects for SSc lung disease, as detected by increased values of DLCO/lung volumes (3), but hardly anyone believes in this therapy today. This is probably a reflection of the weak design and lack of methodological credibility of most studies performed in SSc.

There are several reasons for this situation. First, the natural history of the disease is not well known, and therefore slow disease progression due to the disease itself could be spuriously considered as stabilization due to the therapy for some patients, while for patients with an unfavourable disease profile at entry regression-to-the-mean is a problem in uncontrolled studies (6). Second, the duration of follow-up in patients receiving a therapeutic intervention under evaluation is usually short. Third, the small numbers of patients per cohort do not favour the adoption of randomized controlled studies, and whenever such studies are undertaken, small sample sizes are the rule (7). Finally, surrogate markers are used for the response instead of hard clinical outcomes, and these surrogates have their limitations. Nevertheless these surrogate markers probably represent very early changes of lung function, in a time point when the involvement of the lung can regress without serious consequences for the health of the individual. Therefore these markers have been proposed for future studies in the Portonovo Conference on the evaluation of patients with systemic scleroderma (8). At the same time, very little progress has been made at the basic science level to suppress fibrotic processes.

Airo *et al.* in this issue of the journal (9) report their experience with intravenous cyclophosphamide therapy for SSc PIF in a retrospective, observational study. They also attempted to enhance their findings by reviewing five other relevant studies (10-14). However, they were not able to adopt a standard protocol and use standardized individual level data from all the previous cohorts. Pooling was performed on the data of 3 of the 6 studies. The endpoint of the study by Airo *et al.* was alterations in lung function tests after 6 months (9). The regimen used was cyclophosphamide 750 mg pulses combined with methylprednisolone 125 mg pulses every 3 weeks and the results were promising.

Despite the small numbers, lack of prospective or even retrospective control subjects, and the limitations of retrospective evaluation, practically all the studies reporting the results of cyclophosphamide therapy in SSc PIF have suggested that cyclophosphamide may be more or less efficacious for PIF. However, the outcomes have not been the same between studies, the prednisolone dose differs significantly between them, and the baseline characteristics of the patients are considerably different across studies. For instance, the patients in the study of Pakas *et al.* (12) had considerably advanced disease at the initiation of treatment, while the patients in the study by Giacomelli *et al.* (14) had initial FVC levels within normal range. While the results are promising, the need for caution cannot be overstated.

There are several issues regarding the definition of the disease and outcomes thereof that have to be considered in future studies (15). First, what is the histopathologic subset of fibrosing alveolitis in patients with SSc? It is well known today that non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) are two histopathologic types with different outcomes, and they may coexist in patients with scleroderma lung disease but to a different extent from one patient to another (16). Second, is PIF clinically significant? Pulmonary function tests and dyspnea scoring are the only widely available means of determining whe-

ther the disease is sufficiently severe to justify immediate therapeutic intervention (15). Third, is biopsy warranted? It seems that the histopathological subset has some prognostic significance for early disease, but not for end-stage disease (16). Fourth, does high resolution CT (HRCT) have an important prognostic role? It appears that ground-glass attenuation is more often indicative of fine intralobular fibrosis in NSIP, and is strongly suggestive of reversible disease only in those cases without coexisting traction bronchiectasis or reticular abnormalities (17,18). Therefore the distinction between ground glass and reticular abnormalities is important in order to evaluate therapeutic interventions. Fifth, does bronchoalveolar lavage (BAL) have an important prognostic role to play? It has been suggested that BAL neutrophilia can be linked to more progressive disease but other studies have shown that BAL neutrophils do not predict clinical outcomes in patients treated with immunosuppressive agents, and therefore BAL does not seem to be very important as an outcome of therapy (16). All of these issues need to be settled in order to select appropriate outcomes and collect the appropriate information at baseline and during follow-up on important predictors and correlates of outcomes.

Despite their limitations, the studies regarding therapy for SSc/PIF have taught us important lessons. They show that in order to settle our uncertainties, we should undertake multi-center, cooperative studies using standard protocols to evaluate therapeutic interventions for SSc. Guidelines for clinical trials on scleroderma have been already published and should provide an impetus for such efforts (19). These guidelines have not yet been used to evaluate therapeutic interventions for SSc/PIF, perhaps because of the perceived lack of effective or highly promising agents for halting fibrotic processes. Given the limited available evidence to date, the most promising agent available today seems to be cylophosphamide taken either orally (20) or in intravenous pulses, and its efficacy should be evaluated in larger controlled trials. Preferably, therapeutic interventions should start early at the stage of fibrosing alveolitis, when the chances of having an impact may be better. Consecutive and careful evaluation of pulmonary function is warranted and long-term follow-up should be encouraged, in order to document both the efficacy and the tolerability of the tested regimens. Finally, basic and pre-clinical research to develop new therapeutic agents aimed at inhibiting fibrosis should be one of the main targets of scleroderma research in the future.

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